

Review on application of Carbon Nanotube for treatment and diagnosis of Alzheimer Disease

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Abstract

The development of abnormal protein aggregates, such as tau tangles and beta-amyloid plaques, in the brain is a hallmark of Alzheimer's disease (AD). For AD to be effectively managed and treated, early and correct diagnosis is essential. Because of their distinct structural and electrical characteristics, carbon nanotubes (CNTs) have become a viable option for the identification and treatment of Alzheimer's disease. Carbon atoms arrange themselves in hexagonal patterns to form the cylindrical structures known as carbon nanotubes. Their remarkable mechanical, thermal, and electrical characteristics make them perfect for a wide range of uses, including biosensing. With their large surface area and ability to be functionalized with certain proteins, CNTs can interact with biological entities very selectively and sensitively. The review paper aims to study on recent diagnosis and treatment of Alzheimer's disease with the help of nanomaterial i.e Carbon Nanotubes. Despite the enormous potential, there are still obstacles that must be overcome before using carbon nanotubes to diagnose Alzheimer's disease. Standards must be satisfied, detection techniques must be optimized, and comprehensive validation is required. To overcome current obstacles and move CNT-based diagnostic tools closer to clinical deployment, multidisciplinary teams must continue their research and work together.

Key Words: Carbon Nanotube, Alzheimer's disease, Neurodegenerative, Nanomaterial.

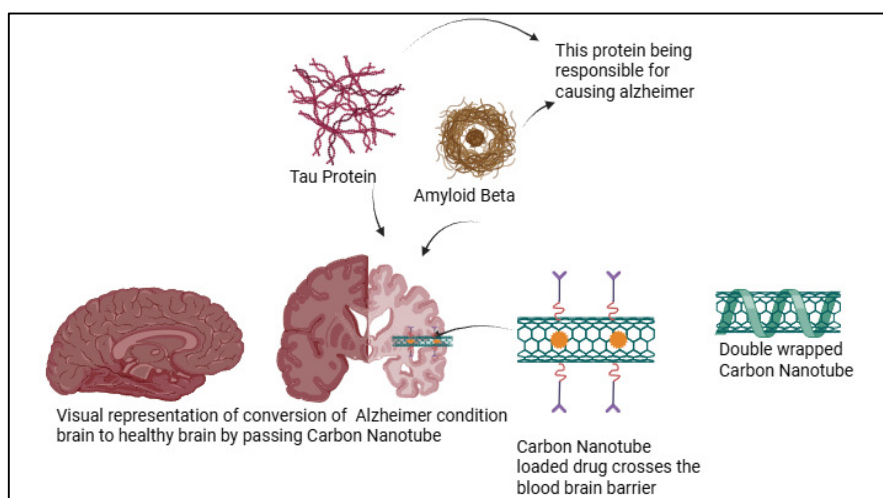


Figure: The Graphical Abstract

1. Introduction

Determining the pharmacological and toxicological characteristics of the new generation of nanomaterials is crucial to their effective application as drug carriers in the treatment of Alzheimer's illnesses [1]. The Alzheimer's Association estimates that in developed nations, 13% of those over 65 have AD. For patients of this age, it ranks as the seventh most common cause of death [2]. The present treatments for AD are symptomatic and the etiology is unknown. Neurotransmitter or enzyme replacement therapy is the current standard of care for AD patients with cognitive impairment. These include antioxidants, amyloid-targeted medications, nerve growth factors, acetylcholinesterase inhibitors, and other medications that offer a variety of symptomatic advantages. It appears that neither the treatment nor the progression of AD can be halted by any of the currently available options. By enabling targeted drug administration and improving the bioavailability and efficacy of many medications and other bioactive substances, nanotechnology may offer a potential way around several challenges in the treatment of AD [3]. The central nervous system (CNS) access is the primary obstacle to the accurate diagnosis and treatment of neurological illnesses. The blood-cerebrospinal fluid barrier (BCSFB) and the blood-brain barrier (BBB) are two physical and biochemical dynamic barriers that primarily restrict the distribution of medications and imaging agents to the nervous system. The central nervous system (CNS) is completely sealed off from the unstable blood environment by these barriers. For the diagnosis and effective treatment of Alzheimer's disease, new therapeutic methods that target the central nervous system (CNS) are required [4]. For neurological applications, one of the most appealing approaches is the utilization of carbon nanotubes (CNTs). Thus, there is hope that the development of nanotechnology will transform the identification and management of CNS illnesses [5]. AD was found more than a century ago, but its exact etiology is still unknown. The etiology of AD has been proposed and accepted to include a number of physiological abnormalities or changes, such as excitotoxicity, cholinergic imbalance, tau hyperphosphorylation, extracellular A β plaque, mitochondrial dysfunction, etc as well as risk factors, such as aging, genetic mutation, environmental factors, etc [6]. Anormal synthesis of Acetylcholine leads to neuron degeneration [7] whereas accumulation of Amyloid β in brain causes nerve necrosis also leads to neurodegeneration [8].

Looking into Tau Proteins, is a microtubule-associated, highly soluble protein that is primarily expressed in central nervous system neurons, including glial cells, astrocytes, and peripheral nerve cells. Stabilizing the microtubule assembly and aiding in the stability of nerve cells are the main functions of the tau protein. Crucial elements of the neural cytoskeleton, microtubules serve as a belt of transport for different granules, vesicles, chromosomes, and cell organelles including mitochondria [9]. This protein is present in mainly four areas acidic region, protein rich region, microtubule binding region, C-terminal [10]. Inflammation in astrocytes and microglia shows the impact on AD. Microglia, which make up 10–15% of brain cells, are essentially macrophages of the brain or central nervous system. Research showed that the AD brain's microglia were substantially more active than those in the normal brain [11]. This review paper primarily addressed the usage of carbon nanotubes in the diagnosis and treatment of Alzheimer's disease to overcome several obstacles.

2. Carbon Nanotube

Carbon nanotubes, also known as engineered nanoparticles (NPs), are made of graphene, a single atom-thick carbon sheet. They can be either concentric multiple sheets (ranging from 2 to 50) held together by van der Waals interactions, or they can be single rolled sheets, known as single-walled (SWCNTs) (MWCNTs). Polymers, rubbers, and composite

materials can have their structural qualities improved thanks to the morphological and physicochemical characteristics of carbon nanotubes [12]. While SWCNTs and MWCNTs differ significantly in diameter, measuring between 1-3 nm and 10–200 nm, respectively, their lengths, which span from a few hundred nanometers to many tens of micrometers, are comparable. These designed NPs' remarkable properties are recognized by their extraordinarily high length-to-diameter ratio, or aspect ratio. Several kinds of techniques that have been refined throughout time are used to synthesize CNTs, with varying degrees of purity and yield [13]. These consist of: i) electric arc discharge in atmosphere of inert gas created by helium or argon; ii) laser ablation; and iii) chemical vapor deposition (CVD) with metal catalysts like iron, nickel, and cobalt or rare-earth metals and hydrocarbons as carbon sources (acetylene, propylene, ethylene, or methane) [14].

The drug can be loaded into a carbon nanotube (CNT) through four different mechanisms: physical adsorption via non-covalent hydrophobic interaction; encapsulation within the CNT; functionalization of the drug on the CNT surface; and, in certain cases, drug loading into another carrier with the CNT functioning as a release controller. CNTs are taken in by cells by

passive diffusion and endocytosis. They can successfully be used as nanocarriers treating brain gliomas and CNS diseases since they can pass the blood-brain barrier. Through receptor-mediated endocytosis, transcytosis, needle-like transport, or passive transport, CNT traverses the blood-brain barrier [15].

2.1 Types of Carbon Nanotube

2.1.1. Single-Walled Carbon Nanotube- The initial description of single-walled carbon nanotubes (SWNTs) dates back to 1993 [16]. A single layer of graphene sheet with a diameter of 1-2 nm makes up SWNTs. The exterior and inside views of a SWNT are displayed in Fig. 1. To prepare CNTs for proper control over improvement and atmospheric state, a catalyst is necessary. The length of a CNT might vary according on the preparation techniques, resulting in less purity.

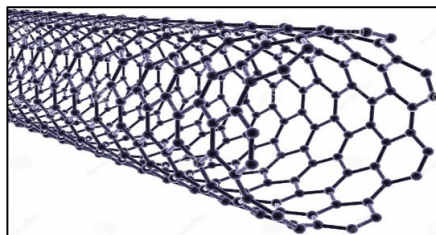


Fig.1 Single-Walled Carbon Nanotube

2.1.2 Double-walled carbon nanotube

Combination of two tube of carbon form double-walled carbon nanotubes (DWNTs), which may be identified from one another by the outer tube enclosing inner tube. The inner tube is 1-3 nm in diameter, whereas the outer tube is 2-4 nm. The surface and internal views of double-walled carbon nanotubes are displayed in Figure 2.

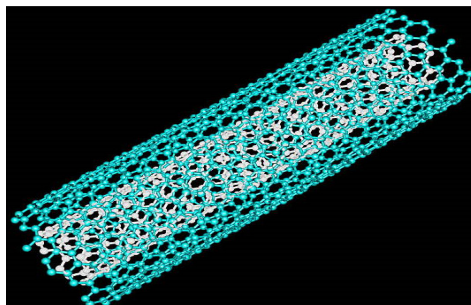


Fig.2 Double-Walled Carbon Nanotube

2.1.3 Multiwalled Carbon nanotube

Because graphene sheets with varying diameters ranging from 2 to 50 nm are present in many layers. MWNTs are also numbered and named based on the fact that graphene sheets exist. The tube's outer layer radius ranges from 2 nm to 20–30 nm, while its inner layer radius is 0.34 nm [17,18].

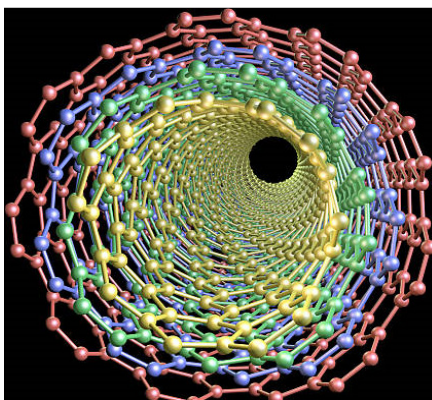


Fig.3 Multi-Walled Carbon Nanotube

2.2 Carbon Nanotube Cells Reuptake Mechanisms

Although the cellular uptake of carbon nanotubes (CNTs) has been confirmed by numerous studies, it is still unknown how CNTs enter cells and function [19]. To facilitate additional functionalization with the intended therapy, the CNTs must first be modified. Acrylamides, hydrochloric and nitric acids, and polymers, polyethylene glycol lessen the cytotoxic effects before medication loaded. After that, the medications can be unloaded from the CNTs after they've arrived at their target.

To help the target cells absorb the carbon nanotubes, targeting ligands or recognition units are also attached to the CNTs. To track the carbon nanotubes inside body, a tracking agent—such as a fluorescently tagged ligand—is also affixed to the CNTs [20].

Cellular uptake of CNTs can also be monitored using cutting-edge microscopic methods like TEM and AFM. Cells absorb carbon nanotubes by passive and endocytosis-independent processes [19].

The CNTs' ability to permeate cell membranes is improved by the size and surface charge of the functional groups on their surface. There are several ways to provide carbon nanotubes to the body, including oral, nasal, subcutaneous, abdominal, intratracheal, intramuscular, intracerebral, and intravenous. The length of the CNTs affects the absorption mechanism as well [21].

Carbon nanotubes with a diameter less than 1 μm can be readily internalized by cells. When taken orally, shorter CNTs are readily absorbed by the body through the intestinal columnar cells. Before diffusing from the injection site into the lymphatic system, CNTs are administered subcutaneously and linger there [22].

2.3 Bio-medical Application of Carbon Nanotube

2.3.1 Therapeutics Application

2.3.1.1 Drug and Gene Delivery

To treat a wide range of illnesses, CNTs have been used in the creation of numerous drug delivery systems. Carbon nanotubes are good nanocarriers for drug delivery because of their special qualities, which include a large surface area, great mechanical strength, appropriate chemical stability, and a high drug-loading capacity [23]. Because CNTs are sensitive to the tumor microenvironment, their toxicity and adverse effects can be reduced [24,25]. The tumor cells' resistance to several drugs, the inhibition of cell division, and the cell cycle of the impacted cancer cells can likely be decreased by applying a CNT-based framework. Peptide-modified SWCNTs have demonstrated improved tumor targeting and strong anti-tumor activity [26].

2.2.1.2 Carbon nanotubes for drug delivery across the blood-brain barrier- Although it is difficult for drugs to pass through the blood-brain barrier, drug delivery to the brain is problematic (BBB). Functionalized carbon nanotubes may be able to target the brain, according to some recent research [27]. They have inherent optical and thermal properties in contrast to other nanocarriers. Furthermore, functionalized carbon nanotubes are the best nanocarriers for brain targeting because of their capacity to penetrate through biological barriers through transcytosis and passive processes [28].

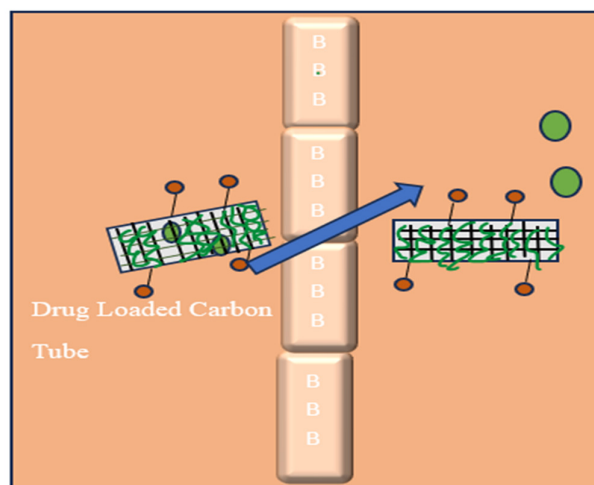


Fig.4 Schematic Representation of Drug crosses the blood-brain barrier and releases a drug

3. Diagnosis of Alzheimer's disease by Using Carbon Nanotube

3.1. Carbon nanotube field-effect transistor (CNT-FET) biosensors- One particular type of biosensor that uses carbon nanotubes as the sensing element is the carbon nanotube field-effect transistor (CNT-FET) biosensor. The special electrical and mechanical characteristics of carbon nanotubes make them ideal candidates for biosensing. Because of its great sensitivity, low power consumption, and capacity to detect a broad variety of biomolecules, CNT-FET biosensors hold great promise. A CNT-FET biosensor's working concept is based on how the presence of biomolecules alters the carbon nanotube channel's electrical conductance fig.3.1.1 The charge density of the carbon nanotube is changed when biomolecules attach to its surface, and this modification affects the nanotube's electrical conductance. The biomolecules may be identified and measured thanks to the ability of a gate electrode placed near the carbon nanotube to sense changes in electrical conductivity. Nowadays, based on target-receptor interaction, CNTs arranged as FETs are used to translate bio/chemical charge changes into electrical signals for in vitro and in vivo applications. These consist of proteins, pH, and nucleic acids, which are helpful biomarkers for the diagnosis of AD [29,30,31].

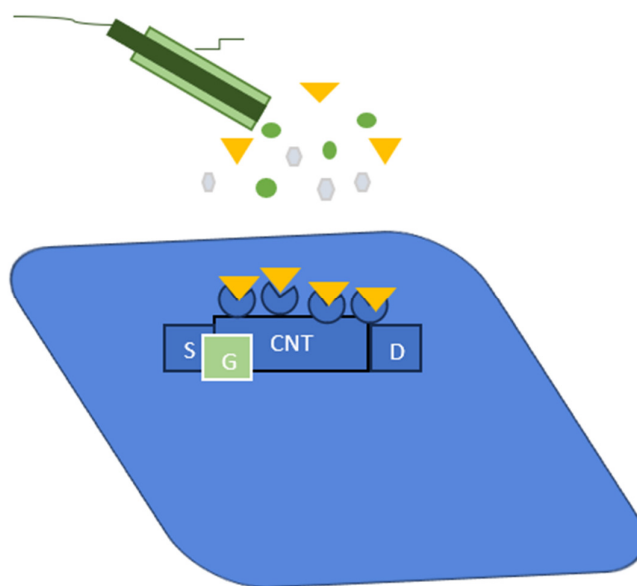


Fig.5 Basic principles of CNT-FETs with electrodes for the source (S), drain (D), and gate (G).

3.2 Carbon Nanotube Based Field-Effect Transistor Biosensors

To overcome these difficulties, scientists created very uniform semiconducting carbon nanotube (CNT) thin film biosensors using field-effect transistors (FETs) [32]. The mass-produced CNT FET sensors outperformed previous technologies reported to date in enabling accurate and reproducible sub-femtomolar detection of A β 42 and A β 40 peptides in whole human serum when paired with oligonucleotide aptamers as effective bio-receptors. The biosensors achieved selectivity ratios of up to 730% (A β 40) and 800% (A β 42) by employing numerous blocking processes to decrease the adsorption of biological substrates to the sensor. The broad dynamic range (>10⁴), quick reaction time (few minutes), and low variation (<10%) of the aptamer-functionalized CNT FET biosensors made them suitable for use as an affordable and quick clinical detection method for the early diagnosis and mass screening of AD. This platform might assist in bringing pricey, sophisticated diagnostic instruments from laboratories to the point of care.

The capacity of these biosensors to identify biomarkers for Alzheimer's disease in both 1 \times PBS and unadulterated human serum was evaluated. With ultralow LODs of 45 aM and 55 aM for A β 40 and A β 42, respectively, the results demonstrated the broad analytical range of the aptamer-functionalized CNT FETs [33].

3.3 Electrochemical biosensor

The simplicity of their manufacturing, low cost, mobility, and high sensitivity make electrochemical platforms popular for use in the detection of A β and Tau [34]. An electrochemical sensing system usually has two primary components: a biological recognition element that preferentially reacts with the target (such as an antibody, enzyme, or nucleic acid), target molecules and an electrode that acts as a signal transducer to transform the target analyte's molecular recognition into an electrical signal. The electrode has undergone a number of chemical modification techniques, such as the addition of functional nanomaterials, to increase the signal transduction efficiency [35,36].

One another electrochemical biosensor was developed using 70 single-walled carbon nanotubes (SWCNTs) to measure Cu²⁺ and A β simultaneously. The glassy carbon electrode (GCE) served as the foundation for the biosensor, which was engineered to generate a stable colloidal suspension A B C, promote CNT stability and electron transport, and accomplish a dense and homogenous distribution of surface functional groups. The subsequent assembly of negatively charged ABTS and recognition components required the functionalization of SWCNTs with poly (diallyldimethylammonium chloride) (PDDA) and 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulphonate) (ABTS) [37].

3.4 Interdigitated microelectrode (IMEs)-based impedimetric biosensor

A clinical diagnostic tool for Alzheimer's disease (AD) that uses dielectrophoretic (DEP) force and polystyrene beads (PS) in an interdigitated microelectrode (IMEs)-based impedimetric biosensor [38]. When comparing the biosensor's sensitivity to the reference without PS and DEP force, it was over two times higher when measuring A β and tau in 1% standard plasma and phosphate-buffered saline (PBS). The biosensor's ability to distinguish between clinically diagnosed AD patients and normal controls was demonstrated by its great accuracy ($p < 0.0001$) in identifying the amounts of A β and tau in clinical plasma samples. Using PS that was altered with DEP forces, the study was able to identify AD by multiplexing tau and A β in blood samples. A change in the biosensor's impedance resulted from the concentration of the PS coated with tau or A β employing either positive or negative DEP pressures. For A β and tau, the biosensor showed 3.06- and 2.40-times higher sensitivity in PBS and 5.74- and 2.51-times higher sensitivity in standard plasma, respectively. With a high degree of accuracy ($p < 0.0001$, one-way ANOVA), the biosensor was able to distinguish AD patients from healthy controls. While other research has identified AD biomarkers using nanoparticles, this work is the first to use biosensors that combine PS and DEP forces to detect A β and tau with great sensitivity to diagnose AD in clinical plasma samples [39,40].

3.5 Tau and Amyloid Beta Proteins in Alzheimer's Disease: An Optical Biosensor

Due to their capacity to provide label-free, real-time, and direct detection of biological targets, optical biosensors offer a number of advantages over conventional analytical techniques, including high specificity, sensitivity, small size, and efficiency. In a typical optical biosensor, an optical transducer system is integrated with a biorecognition detecting element to provide a signal equal to the amounts of analytes [41]. The use of colorimetric, fluorescent, surface-enhanced Raman scattering (SERS), and localized surface plasmon resonance (LSPR) biosensors in the early diagnosis of AD [42].

4 Treatment of Alzheimer's disease by using Carbon Nanotube

Carbon-based nanostructures are becoming more significant in the field of neuroscience because of their special chemical and physical characteristics. Carbon nanostructures have lately acquired enormous significance due to the existence of several carbon allotropes such as graphite, carbon nanotubes (CNTs), fullerene, and graphene. Of these carbon family

nanomaterials, carbon nanotubes (CNTs) have been widely used in various biomedical and pharmaceutical applications, such as targeted drug delivery, imaging, tissue engineering cancer therapy, and diagnosis, due to their desirable features [43].

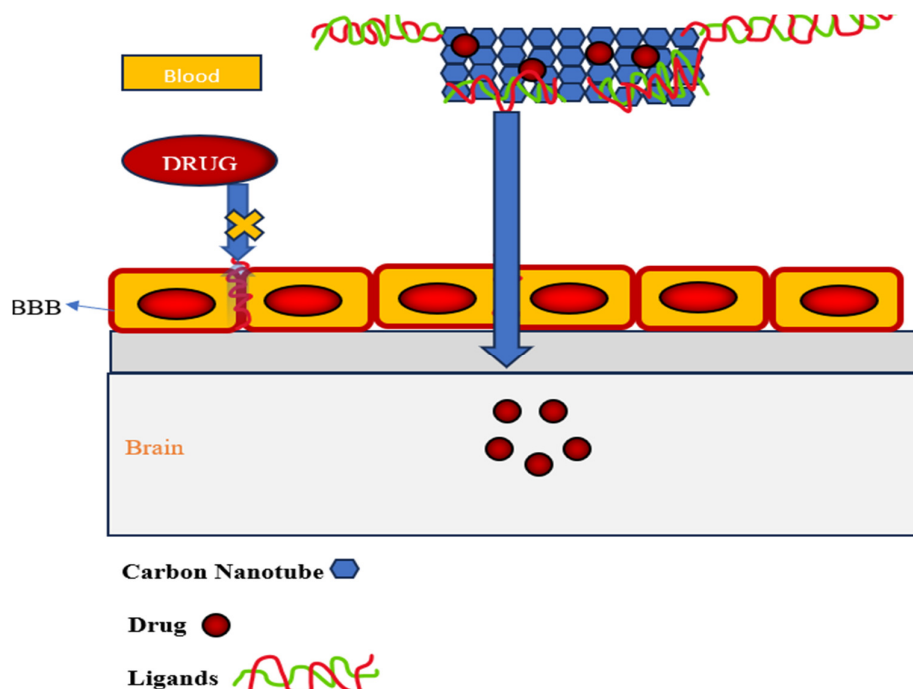


Fig.6 Illustrates the diagrammatic picture of drug transport to the brain aided by carbon nanotubes. The majority of aqueous solvents do not dissolve CNTs in their pure or unaltered state. Chemical modification or surface functionalization may improve the solubility in water, which will allow for their use in the treatment of neurological diseases [44].

Since carbon nanotubes (CNTs) in their native condition do not dissolve in water, their use in nanomedicine is complicated. Clinical experiments, however, demonstrate that CNTs are harmful in their natural habitat. However, their exposure, dosage, and mode of administration determine their effectiveness and adverse effects. By using surfactants to coat carbon nanotubes, one can lessen the toxicity of the nanotubes to cells and hence the interaction between the cells and the CNTs. The application of metal-catalyzed produced carbon nanotubes and their formation of free radicals, peroxidative reactions, DNA damage, and inflammations are barriers to their use in the diagnosis and treatment of neurological illnesses [45].

5 Future Perspective

The primary goal of the review is to use carbon nanotubes to detect and treat Alzheimer's disease. However, in the future, treating diseases with carbon nanotubes may present additional

challenges due to issues with poor drug solubility, cytotoxicity, cellular drug distribution, drug inaccessibility into cell membranes, tissue damage, etc.

6 Conclusion

Alzheimer's disease and other neurodegenerative diseases can be detected and treated with the help of carbon nanotubes. When it comes to meeting fundamental physics requirements at non-metric scales, carbon nanotubes usher in a new era of practical applications. Through their endless applications in electronics, chemistry, and nearly exclusively in the biomedical field, they offer incredibly peculiar applications to the upcoming generations. Within the realm of biomedicine and therapeutics, carbon nanotubes are a type of nanomaterial with many essential uses. Furthermore, the advancement of nanotechnology has been instrumental in resolving the constraints and laws that accompanied silicon microelectronics. Because of its special structural, electrical, and mechanical qualities, carbon nanotubes (CNTs) can be extremely important from every angle of discovery.

7 Reference

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